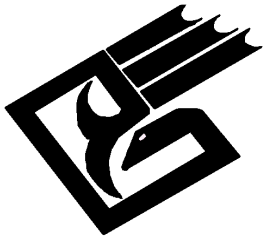

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Faculty of Medicine

Thesis of Medical Degree

The Correlation Between Helicobacter Pylori infection and Lipid Profile in Bushehr Healthy Heart Study In 2009-2010

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بسم الله الرحمن الرحيم

سپاس خدای را که هرچه دارم از اوست ...

حمدوسپاس ایزد حکیم که شور گام نهادن درمسیر علم طبابت را عطایم نمود و

سلام و صلوات بر پیامبراکرم(ص) ختم رسل و دوازده خورشید عالم تاب آسمان امامت و ولایت و درود بیکران بر طلایه داران طریق ادب وفضیلت و جویندگان حق وحقیقت.

سپاس بیکران به درگاه حق که پنجره ای به بیکران وسعت دریای علم و اندیشه و معرفت برویم گشودو به همنشینی رهروان علم ودانش مفتخرم نمود .

شکر می گویم طلوع روزی که تاریکی جهل را ازمن زدودی وآفتاب علم را بر وجودم تاباندی؛ که ازالتهابش همیشه سرگردان و حیران دربیابان طاقت فرسای زندگی، سر ازپا نشناخته جستجوگر باشم.

تورا سپاس که از روی کرم پدرومادری مهربان نصیبم ساختی تا درسایه درخت پربار وجودشان بیاسایم وازریشه آنها شاخ وبرگ گیرم ودرسایه وجودشان در راه کسب علم ودانش تلاش نمایم. والدینی که بودنشان تاج افتخاری ست برسرم ونامشان دلیلی ست بربودنم. آموزگارانی که برایم زندگی؛ بودن و انسان بودن را معنا کردند.

حال این برگ سبزی ست تحفه درویش تقدیم آنان...

این مجموعه را به پدر و مادر عزیزم تقدیم می کنم

I share this work with my family, particularly my parents; whose encouregment and strength have guided and enable me throughout my entire academic career. Their support, love, sacrifices and encouregment have helped to make my success possible.

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With Get Well Wishes for Patients…

Abstract

Introduction: Helicobacter pylori(H.pylori) is the most common infection throughout the world, with a higher prevalence in developing contries.This infection is reported to be associated with many extragastrointestinal diseases, such as cardiovascular disease. Among the studies that have suggested a relationship between H.pylori infection and coronary heart disease, some of the underlying mechanisms still need to be discovered. It has been reported that chronic H.pylori infection results in lipid alterations that could partially contribute to the initiation and development of coronary atherosclerosis.This study is design to investigate the correlation of H.pylori seropositivity and lipid profile in a cross sectional population based study.

Methods: We selected 1754 patients(50.8 % females, 49.2 % males),older than 25 year old , randomly from MONICA Healthy Heart project. Sera were screened for IgG antibobies against H.pylori with an ELISA and the samples were considered positive with IgG values higher than 30 RU/ml.

Result: The prevalence of H.pylori seropositivity was 61.57% in the studied population. At first there was a correlation between H.pylori and decreased HDL-c (P = 0.042)and increased TG (P = 0.01) in primary unadjusted analysis, however, after age and sex adjustment only association between H.pylori and decreased HDL-c remained significant (P = 0.040 ; OR=1.23, 95%CI: 1.0-1.50).But at the end multiple logistic regression analysis showed no more correlation between H.pylori seropositivity and HDL-c & other lipid profiles.

Conclusion: In this large population based study that was designed in Northern Persian Gulf cities , no correlation between H.pylori infection and lipid profile demonstrated among men and women.

Key Words: H.pylori, atherosclerosis, HDL-cholestrol, LDL-cholestrol, dyslipidemia, cardiovascular disease, metabolic syndrome

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INTRODUCTION

Atherosclerosis

Atherosclerotic disease is the leading cause of death world wide ,[i] and almost half the disease burden in developing countries is due to noncommunicable diseases, including cardiovascular disease.[ii] It `s a chronic inflammatory disease that affects all arterial beds and can present with multiple clinical manifestations according to the end organ supplied , such as coronary artery disease and peripheral artery disease.[iii] It primarily involves the intimal layer of the artery wall, however other forms of arteriosclerosis largely can involve other layers of the wall, for example Mönckeberg's arteriosclerosis,which is characterized by calcification of the medial layer.[iv]

This systemic disorder is characterized by plaque formation at selected sites of the arterial tree,that in adults commonly noted in the coronary arteries, at the carotid artery bifurcation, and in the infrarenal aorta and leg arteries.[4]

The basic mechanism was first proposed well over a century ago by Von Rokitansky and Virchow and was recently reviewed by Ross,[v] plaque formation

is thought to begin with vascular injury and to involve inflammation, vessel remodeling, and accumulation of lipid in the subendothelial space.[4]

Inflammatory markers in the blood that have been associated or correlated with risk of cardiovascular disease include highly sensitive C-reactive protein(CRP) , serum amyloid and interleukins(IL-6) , tumour necrosis factor-α(TNF-α) , and vascular and cellular fibrinogen adhesion molecules.[5]

In humans, no single factor can account for all the causes of coronary artery disease(CAD), it`s caused by multiple factors .[5]

Nowadays it is necessary to gain better understanding about pathogenesis of human atherosclerosis and relevant genetic and pharmacological factors. Although diabetes mellitus, hypertension, smoking, hyperlipidemia and genetic predisposition are the major known risk factors for the development of atherosclerosis, a substantial proportion of patients with atherosclerosis have none of these traditional risk factors and it may occur in the absence of them.[5 , vi]

Atherosclerosis and Infections

Novel risk factors contributing to initiation and progression of atherosclerosis include inflammation and infections.[6]

As some studies have found the association of elevated levels of C-reactive protein and future risk of coronary heart disease and stroke, supporting the hypothesis that inflammation plays a role in the pathogenesis of atherosclerosis.[6, vii] This role of chronic inflammation as a suggested cause of high morbidity and mortality in the patients by acceleration of atherosclerosis has received considerable attention in recent years.

There is also some data that have suggested the possible potential role of some infectious agents in the pathogenesis of atherosclerosis.[viii]

In a study that was done by Dr.Vahdat and colleagues in this center,it was showed that beyond traditional cardiovascular risk factors,concomitant chronic infection and elevated CRP were significantly correlated with coronary artery disease in general population.[ix]

The association between atherosclerosis and infectious diseases is based on 3 main sets of evidence: epidemiological, pathological and microbiological. The evidence to support causality includes in vitro data biologic plausibility, and data from animal models and clinical trials.[5, x]

There are a large number of different infectious agents that have been suggested, with an increased risk of cardiovascular disease. These include:Chlamydia pneumoniae, Porphyromonas gingivalis, Helicobacter pylori , influenza A virus, hepatitis C virus, herpes virus, hepatitis B virus, Epstein-Barr virus,

Mycobacterium tuberculosis, cytomegalovirus, and human immunodeficiency virus.[xi,xii,xiii,xiv]

However, there are significant differences in the strength of the data supporting their association with cardiovascular disease pathogenesis. In some cases, the infectious agents are found within the plaques and viable organisms can be isolated suggesting a direct effect. In other cases, the association is entirely based on biomarkers.[8,xv,xvi]

There are several possible ways in which infectious agents may induce or accelerate atherosclerosis .These include:

• molecular mimicry of microbial heat shock protein-60, inducing an autoimmune reaction;[5]

• local release of endotoxin (lipopolysaccharide), which may increase cholesterol ester uptake by macrophages to form foam cells;[15]

• direct invasion of the vessel wall causing an inflammatory response, which leads to a local increase in lymphocytes and macrophages and production of cytokines and tissue growth factors;[xvii]

• indirect systemic effect of remote infections causing systemic release of lipopolysaccharide, causing damage to the endothelium, systemic increase in cytokines, with activation of inflammatory markers, and stimulation of procoagulants, leading to thrombosis and acute ischemia ; and [7,17]

• induction of changes in lipoproteins by cytokines, which indirectly predisposes patients to atherosclerosis. For instance, a secondary increase in low-density lipoprotein(LDL) levels and a decrease in high-density lipoprotein (HDL) levels may be induced, resulting in pre-atherosclerotic conditions.[15]

Among many underlying mechanisms that have been proposed about infectious diseases cause atherosclerosis; most of them suggested that it may trigger the process of atherosclerosis by direct or indirect inflammatory effects, especially at younger ages; although nothing has ever been conclusively proven.[8,15]

Among investigations, association of chronic infection with C pneumoniae, H pylori and cytomegalovirus (CMV) infections and CAD, are worked more.[xviii,xix] That the association between C pneumoniae and CHD is stronger and the association between CHD and H pylori maybe accounted for residual confounding from risk factors .[xx, xxi]

Helicobacter Pylori

Helicobacter pylori (H. pylori) infection is the most common infection worldwide that affects more than half of the world population,[xxii]H.pylori infection prevalence varies between countries; generally, the prevalence is about 30% in developed and up to 80% in developing countries,[xxiii] and increases with age. [xxiv, xxv] H.pylori is a

gram negative, spiral-shaped pathogenic bacterium that specifically colonizes in the gastric epithelium and causes chronic and active gastritis, peptic ulcer disease and is associated with gastric adenocarcinoma.[xxvi]

This infection induces an acute polymorph nuclear infiltration in the gastric mucosa. If the infection is not effectively cleared, this acute cellular infiltration gradually replaced by an immunologically mediated and chronic mononuclear cellular infiltration,[xxvii] that characterized by the local production and systemic diffusion of proinflammatory cytokines,[xxviii] and may exert their effects in remote tissues and organic systems and result in extragastric manifestations.[xxix]

Diagnosis of H.pylori can be achieved by taking biopsies by endoscopy. However, this procedure is invasive and might not give accurate results if colonization is patchy. [xxx] For population screening, serodiagnosis remains one of the methods of choice for detecting the prevalence of infection. [xxxi] The technique of choice is currently enzyme-linked immunosorbent assay(ELISA) because it is a simple, quick, and low-cost technique that permits immunoglobulin class-specific determinations.[xxxii]